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Cancer Risk Following Treatment of Childhood Cancer

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Many children with cancer have experienced long-term survival and even cure with advances in chemotherapy and radiotherapy. With this success, however, have come late complications of treatment, including sterility, deformities, organ failure (16), hormonal imbalances, psychosocial problems (12), and mental impairment (8,18). Of special concern are the neoplastic sequelae (10), which are evaluated in this study.

The study of long-term effects of therapy for childhood cancer is important for several reasons. An increasing proportion of children are now cured of their cancer and can expect to live many years, during which the long latency periods of carcinogenesis can be expressed more readily than following treatment of adult cancers. Also, in children there are fewer confounding exposures that may contribute to cancer etiology, so the late effects of therapy can be evaluated more easily than in adults. Many pediatric tumors also appear to have a heritable component (20) that may account for some second cancers or may enhance the carcinogenic effects of therapy.

Previous studies of long-term survivors of childhood cancer have demonstrated an elevated risk of second tumors, primarily resulting from radiation therapy (13,14,17). However, in reports of the Late Effects Study Group (LESG), some combinations of tumors appeared related to underlying genetic syndromes (17). Among children, few second neoplasms have been related to chemotherapeutic agents, and in the LESG the use of actinomycin D actually seemed to "protect" against the development of radiation-induced tumors (7). In recent years, new cases of second tumors have occurred and more institutions have joined the LESG, so it seemed advisable to reexamine the risks of second primary cancers in relation to chemotherapeutic agents and radiation therapy.

[1]Other collaborating investigators of the Late Effects Study Group are listed in the Acknowledgments.

METHODS

The case group consisted of 222 survivors of childhood cancer who developed a second malignant tumor at least 2 years after the first tumor was diagnosed and who received treatment at one of the 13 participating centers of the LESG. The interval of 2 years was chosen to exclude simultaneous tumors not likely to be treatment-related. A board of LESG pathologists is currently reviewing the histology of the first and second tumors. For those cases in which tissue was not available, the diagnosis was confirmed by review of medical records and pathology reports.

In order to best select controls for the children who developed second cancers, rosters of long-term survivors were constructed for all children with similar histologies as the first malignancies of the cases. A roster was obtained of 9,170 children who survived at least 2 years after cancer diagnosis. The years of diagnosis ranged between 1945 and 1979. Although this roster was used to select two matched controls per case for detailed comparisons of therapy, it was also possible to evaluate this cohort in its own right. We report here the incidence and risk of second cancers in a defined population of survivors of childhood cancer.

When risk estimates for second primaries were developed, 43 children seen at an LESG hospital only for their second tumor (referral patients) and 12 patients with nonmelanoma skin cancer as a second primary were excluded. The remaining 167 cases were used for all the analyses presented.

Five-year age and calendar-period incidence rates for all cancers were applied to the appropriate person-years (PY) under observation to obtain the numbers of second primary cancers to be expected had these patients experienced the rates prevailing in the general population (19). Since the risk of childhood cancer shows little variation among Western countries (25), incidence rates from Connecticut were employed and assumed to be reasonably representative. The period of observation for calculating the risk of developing a second cancer began 2 years after the diagnosis of the first cancer. Among children in whom no second cancer developed, the end of the period of risk was taken as the date of last contact, that is, the date of death for those who died or the date last known alive. For children who developed a second cancer, other than a nonmelanoma skin cancer, the end of the period of risk was the date the second cancer was diagnosed.

The statistical methods used for risk estimation were based on the assumption that the observed number of second cancers followed a Poisson distribution. Tests of significance and confidence intervals for the relative risk (RR), taken as the ratio of observed-to-expected incident cancers, were calculated using exact Poisson probabilities when the observed number of cases were small; otherwise an accurate asymptotic approximation was used (21). Trends of increased RR over time were evaluated following the methods outlined by Breslow et al. (4).

RESULTS

The number of long-term survivors of childhood cancer and the number of nonreferral cases who developed a second cancer (excluding nonmelanoma skin cancer) are shown in Table 1 by type of first malignancy. The first cancer experience of those who developed a second cancer deviates from the usual distribution of incident cases of childhood cancer (26). Although ordinarily rare, retinoblastoma was associated with many second cancers; almost all the cases had bilateral or familial retinoblastoma. Patients with Wilms' tumor, Hodgkin's disease, and neuroblastoma also contributed relatively large numbers of second malignancies. It is noteworthy that acute lymphocytic leukemia (ALL)

TABLE 1. *Number of children who developed a second primary cancer by histologic type of first childhood cancer*

First childhood cancer (ICDO histology)	No. of children[a]	No. who developed a second cancer[b]
Wilms' tumor (8960)	1,248	28
Hodgkin's disease (9650–9656)	1,036	26
Retinoblastoma (9510–9512)	319	20
Neuroblastoma (9490–9500)	790	19
Ewing's sarcoma (9260)	213	11
Rhabdomyosarcoma (8900–8920)	385	11
Brain, excluding medulloblastoma (9380–9440)	764	11
Medulloblastoma (9470)	285	7
Soft-tissue sarcoma, excluding rhabdomyosarcoma (8800–90, 8980–95, 9120–70, 9560)	550	7
Non-Hodgkin's lymphoma (9591)	423	5
Histiocytosis X (9721–9722)	215	4
Acute lymphocytic leukemia (ALL) (9821)	1,530	4
Teratoma (9080–9084)	155	4
Osteogenic sarcoma (9180–9190)	271	4
Nasopharyngeal carcinoma (8082)	68	2
Adrenal cortical carcinoma (8370)	19	1
Malignant melanoma (8720–8761)	104	1
Hepatoblastoma (8970)	12[c]	1
Acute myeloblastic leukemia (AML) (9861)	74	1
Papillary and follicular carcinoma (8330–8340)	65	0
Gonadal-germ cell (8620–8650, 9060–9073)	126	0
Other carcinomas (8010–8081, 8090–8324)	128	0
Other leukemias (9800–9804, 9840–9860, 9863, 9891)	220	0
Other histologies	170	0
Total	9,170	167

[a] Number of children living 2 or more years after diagnosis of their first malignancy.
[b] Nonreferral cases, excluding nonmelanoma skin cancer as second primary.
[c] Hepatoblastoma/hepatocellular carcinoma.

TABLE 2. *Distribution of second primary cancers among persons treated for childhood cancer, by anatomical site*

Second cancer (ICD8)	No.[a]
Bone (170)	48
Thyroid (193)	23
Leukemia (204–207)	22[b]
Connective tissue (171)	20
Brain (191–192)	14
Digestive (150–159)	12
Genitourinary (180–189)	7
Breast (174)	5
Buccal cavity (140–149)	5
Lymphoma (201,202)	3
Pineal gland (194.4)	2
Skin (melanoma) (172)	1
Respiratory (160–162)	1
Mediastinum (164.3)	1
Orbit (190.1)	1
Pelvis (195.1)	1
Unknown (199.9)	1
Total	167

[a] Nonreferral cases.

[b] Nineteen of the 22 leukemias were acute nonlymphocytic (205.0, 206.0, 207.0, 207.2).

was associated with only four cases of second tumors, although this is a common pediatric neoplasm with a relatively favorable survival rate.

The distribution of second tumors by anatomical site is shown in Table 2. These cancers occurred from 2 to 34 years after the diagnosis of the first tumor. Most common was bone cancer, mainly osteogenic sarcoma, followed by thyroid cancer, leukemia, primarily acute myeloblastic leukemia (AML), and soft tissue sarcomas. This pattern of second tumors is distinctly different from the usual distribution of incident cases of childhood cancer (26).

All Cancers

The RRs of developing a second cancer are presented in Table 3. The 9,170 survivors of pediatric cancer accrued 50,609 PY of observation, and the average follow-up period, excluding the first 2 years, was 5.5 years/child. Overall, 167 nonreferral incident second cancers were observed vs 11.4 expected (RR = 15; 95% CI = 13–17). The risks were highest for cancers arising in bone (RR = 133), thyroid (RR = 53), and connective tissue (RR = 41). Although the risk for leukemia was elevated (RR = 14), most of the expected leukemias in this age range involved ALL, whereas almost all the observed cases had AML (19 of 22). The RR for acute nonlymphocytic leukemia was 28. There was little difference in the risk of developing a second cancer between the 5,021

TABLE 3. *Observed[a] and expected numbers of second primary cancers among all children living 2 or more years after diagnosis of their first malignancy*

Descriptive data	Males	Females	Total
No.	5,021	4,149	9,170
PY of observation	27,071	23,538	50,609
Average follow-up	5.4	5.7	5.5
Average year of diagnosis	1969	1969	1969
Average age at diagnosis	7.0	7.1	7.0

	Males		Females		Total			
Second cancers (ICD8)	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	O/E	95% CI
All (140–209)	79	4.64	88	6.77	167	11.41	15	13–17
Buccal cavity (140–149)	2	0.08	3	0.08	5	0.16	31	10–73
Digestive (150–159)	5	0.18	7	0.13	12	0.31	38	20–67
Bone (170)	29	0.22	19	0.15	48	0.36	133	98–176
Connective tissue (171)	6	0.23	14	0.18	20	0.41	41	24–67
Breast (174)	1	0.001	4	0.33	5	0.33	12	3–31
Genitourinary (180–189)	1	0.28	6	3.59	7	3.88	1.8	0.7–3.7
Brain (191–192)	8	0.51	6	0.40	14	0.91	15	8–26
Thyroid (193)	9	0.12	14	0.31	23	0.43	53	34–80
Leukemia (204–207)	13	0.97	9	0.55	22	1.52	14	9–22
Other	5[b]	2.04	6[c]	1.05	11	3.09	3.6	1.8–6.4

[a] Nonreferral cases.

[b] Mediastinum (164.3), melanoma (172), orbit (190.1), pineal gland (194.4), and pelvis (195.3).

[c] Respiratory (162), pineal gland (194.4), unknown (199.9), Hodgkin's Disease (201), 2 lymphomas (202).

boys and 4,149 girls (RR = 16 and 13, respectively). The overall RR remained relatively constant over the period of follow-up, whereas the absolute risk increased significantly with time, from 1.5 extra cancers/1,000 PY in those surviving 2 to 4 years to 15 extra cancers/1,000 PY for those surviving 20+ years (Table 4).

Among 2+ year survivors, the cumulative probability of developing a second cancer was approximately 12% (SE 1.9%) by 25 years (Fig. 1). The expected cumulative probability based on normal population rates for this age group is only 0.7%. This cumulative risk agrees with previous estimates for 5-year survivors of childhood cancer at the Sidney Farber Cancer Institute (14,15).

Retinoblastoma

The patterns of second primary cancers varied according to the type of initial cancer. This is illustrated for retinoblastoma in Table 5. For the 319 nonreferred children, the excess risk was almost exclusively due to bone cancer (RR = ~1,000) and soft tissue sarcomas (RR = 235). The bone cancers were mainly osteogenic sarcoma. Two cases of pinealblastoma also occurred, a surprising

TABLE 4. *Observed[a] and expected second primary cancers among children treated for childhood cancer by time since diagnosis of first malignancy*

	Time (yr)				
	2–4	5–9	10–14	15–20	20 +
No. starting interval	9,170	5,524	2,288	979	296
Obs.	35	52	42	24	14
Exp.	3.0	3.4	2.5	1.6	0.8
O/E	12	15	17	15	17
PY at risk	21,161	17,897	7,703	2,965	882
Absolute risk[b]	1.5	2.7	5.1	7.5	15

[a] Nonreferral cases
[b] $[(O-E)/PY] \times 10^3$, excess number of cases/1,000 persons/yr.

number, since this tumor is exceedingly rare, with only one case/10^7 persons reported each year (1). Overall there was no trend toward increasing risk of second cancers with longer survival.

Wilms' Tumor

Table 6 shows the pattern of second cancers among 1,248 children treated for Wilms' tumor. Unlike retinoblastoma, elevated risks were seen for several cancers, notably of the thyroid (RR = 136), bone (RR = 127), connective tissue (RR = 84), and gastrointestinal tract (RR = 81). With longer survival the RR increased significantly from 14 in those surviving 2 to 4 years to 47 for those surviving 15 + years ($p = 0.01$).

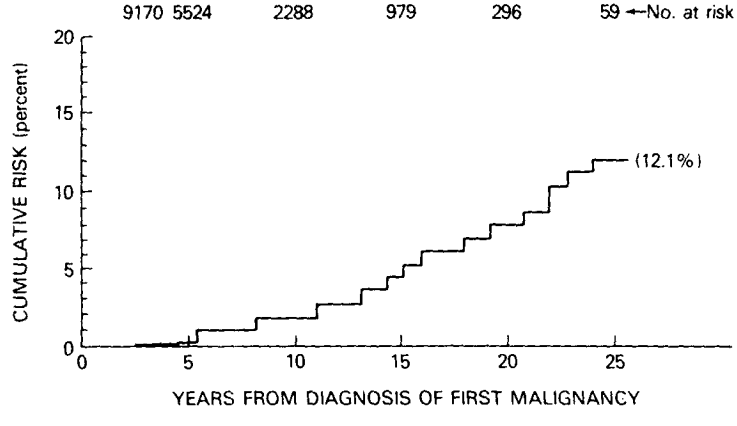

FIG. 1. Cumulative risk of developing a second malignancy among 9,170 persons who survived 2 or more years after the diagnosis of a childhood cancer.

TABLE 5. *Observed[a] and expected numbers of second primary cancers among children living 2 or more years after diagnosis of retinoblastoma*

Descriptive data	Males	Females	Total
No.	166	153	319
PY of observation	1,120	1,117	2,237
Average follow-up	6.7	7.3	7.0
Average year of diagnosis	1968	1968	1968
Average age at diagnosis	1.7	1.7	1.7

	Males		Females		Total			
Second cancers (ICD8)	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	O/E	95% CI
All (140–209)	7	0.158	13	0.174	20	0.332	60	36–93
Buccal cavity (140–149)	0	0.002	1	0.002	1	0.004	—	—
Digestive (150–159)	0	0.005	1	0.003	1	0.007	—	—
Bone (170)	6	0.006	6	0.006	12	0.012	999	515–1,745
Connective tissue (171)	0	0.009	4	0.008	4	0.017	235	64–602
Breast (174)	—	—	0	0.002	0	0.002	—	—
Brain (191–192)	0	0.023	0	0.020	0	0.043	—	—
Thyroid (193)	0	0.002	0	0.006	0	0.008	—	—
Leukemia (204–207)	0	0.048	0	0.032	0	0.080	—	—
Other	1[b]	0.063	1[b]	0.095	2	0.158	13	2–46

[a] Nonreferral cases.
[b] Pineal gland (194.4).

TABLE 6. *Observed[a] and expected numbers of second primary cancers among children living 2 or more years after diagnosis of Wilms' tumor*

Descriptive data	Males	Females	Total
No.	633	615	1,248
PY of observation	4,123	4,103	8,226
Average follow-up	6.5	6.7	6.6
Average year of diagnosis	1969	1969	1969
Average age at diagnosis	3.1	3.8	3.4

	Males		Females		Total			
Second cancers (ICD8)	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	O/E	95% CI
All (140–209)	17	0.549	11	0.601	28	1.15	24	16–35
Buccal cavity (140–149)	0	0.008	0	0.009	0	0.02	—	—
Digestive (150–159)	2	0.016	0	0.009	2	0.02	81	9–293
Bone (170)	5	0.023	1	0.024	6	0.05	127	46–276
Connective tissue (171)	4	0.032	1	0.028	5	0.06	84	27–196
Breast (174)	—	—	0	0.007	0	0.01	—	—
Brain (191–192)	2	0.078	1	0.075	3	0.15	20	4–57
Thyroid (193)	1	0.008	3	0.023	4	0.03	136	36–347
Leukemia (204–207)	1	0.166	3	0.102	4	0.30	13	4–34
Other	2[b]	0.220	2[c]	0.324	4	0.54	7	2–19

[a] Nonreferral cases.
[b] Mediastinum (164.3), pelvis (195.3).
[c] Respiratory (162.9), corpus uteri (182).

Hodgkin's Disease

As shown in Table 7, the 1,036 patients with Hodgkin's disease were prone to bone cancer (RR = 106), leukemia (RR = 89), and thyroid cancer (RR = 68). Most of the leukemias developing as second cancers in this survey were in patients with Hodgkin's disease. The leukemias were all of the acute myelogenous type, so that the RR would be about 140 if population rates for acute nonlymphocytic leukemia (ANL) were used to calculate expected values. There was no trend in risk of second cancers with increasing survival.

Neuroblastoma

As shown in Table 8, the 790 patients with neuroblastoma had an excess risk for cancers of the thyroid (RR = 349), bone (RR = 150), and connective tissue (RR = 73). The RR increased significantly from 7.6 for those surviving 2 to 4 years to 44 for those surviving 15 + years ($p = 0.001$).

Ewing's Sarcoma

Table 9 shows the pattern of risks for the 213 patients with Ewing's sarcoma, with elevated RRs for osteogenic sarcoma (RR = 649) and leukemia (RR = 62). Although based on few cases, the risk of osteosarcoma is almost as high

TABLE 7. *Observed[a] and expected numbers of second primary cancers among children living 2 or more years after diagnosis of Hodgkin's disease*

Descriptive data	Males	Females	Total
No.	663	373	1,036
PY of observation	3,321	2,052	5,273
Average follow-up	4.8	5.5	5.1
Average year of diagnosis	1970	1970	1970
Average age at diagnosis	11.2	13.2	11.9

	Males		Females		Total			
Second cancers (ICD8)	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	O/E	95% CI
All (140–209)	12	0.633	14	1.016	26	1.65	16	10–23
Buccal cavity (140–149)	0	0.011	1	0.010	1	0.02	—	—
Digestive (150–159)	0	0.022	0	0.018	0	0.04	—	—
Bone (170)	3	0.033	2	0.014	5	0.05	106	34–248
Connective tissue (171)	1	0.026	1	0.018	2	0.04	39	5–163
Breast (174)	—	—	0	0.046	0	0.05	—	—
Brain (191–192)	0	0.056	0	0.030	0	0.09	—	—
Thyroid (193)	0	0.022	5	0.053	5	0.07	68	22–159
Leukemia (204–207)	8	0.094	4	0.042	12	0.13	89	46–155
Other	0	0.369	1[b]	0.789	1	1.16	—	—

[a] Nonreferral cases.
[b] Corpus uteri (182).

TABLE 8. *Observed[a] and expected numbers of second primary cancers among children living 2 or more years after diagnosis of neuroblastoma*

Descriptive data	Males	Females	Total
No.	400	390	790
PY of observation	2,429	2,591	5,020
Average follow-up	6.1	6.6	6.3
Average year of diagnosis	1969	1969	1969
Average age at diagnosis	2.4	2.5	2.4

	Males		Females		Total			
Second cancers (ICD8)	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	O/E	95% CI
All (140–209)	9	0.361	10	0.440	19	0.801	24	14–37
Buccal cavity (140–149)	1	0.004	0	0.006	1	0.010	—	—
Digestive (150–159)	0	0.010	0	0.008	0	0.017	—	—
Bone (170)	2	0.013	2	0.013	4	0.027	150	40–386
Connective tissue (171)	0	0.022	3	0.019	3	0.041	73	15–211
Breast (174)	—	—	0	0.010	0	0.010	—	—
Brain (191–192)	1	0.051	0	0.046	1	0.097	—	—
Thyroid (193)	4	0.005	3	0.015	7	0.020	349	140–720
Leukemia (204–207)	1	0.110	0	0.076	1	0.186	—	—
Other	0	0.146	2[b]	0.247	2	0.39	5	0.6–19

[a] Nonreferral cases.
[b] Kidney (189), Hodgkin's disease (201).

TABLE 9. *Observed[a] and expected numbers of second primary cancers among children living 2 or more years after diagnosis of Ewing's sarcoma*

Descriptive data	Males	Females	Total
No.	126	87	213
PY of observation	722	456	1,178
Average follow-up	5.7	5.2	5.5
Average year of diagnosis	1968	1968	1968
Average age at diagnosis	10.9	10.9	10.9

	Males		Females		Total			
Second cancers (ICD8)	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	O/E	95% CI
All (140–209)	6	0.208	5	0.174	11	0.382	29	14–52
Buccal cavity (140–149)	0	0.008	0	0.002	0	0.010	—	—
Digestive (150–159)	0	0.023	0	0.003	0	0.026	—	—
Bone (170)	5	0.007	2	0.003	7	0.011	649	255–1,311
Connective tissue (171)	0	0.007	1	0.004	1	0.011	—	—
Breast (174)	—	—	1	0.006	1	0.006	—	—
Brain (191–192)	0	0.015	0	0.007	0	0.022	—	—
Thyroid (193)	0	0.005	0	0.009	0	0.015	—	—
Leukemia (204–207)	1	0.023	1	0.010	2	0.032	62	8–226
Other	0	0.120	0	0.130	0	0.250	—	—

[a] Nonreferral cases.

as in patients with retinoblastoma, and the risk of leukemia is nearly as high as in patients with Hodgkin's disease.

DISCUSSION

The majority of second cancers in our cohort study were those known to be radiogenic, that is, leukemia, thyroid, and sarcomas of bone and soft tissue (2). These cancers arose in patients whose first malignancy is usually treated with high-dose radiation therapy, and preliminary analysis from our case-control study indicates a significant association between radiotherapy and the risk of second cancer. Thus, we are confident that radiation contributed substantially to the excess of second tumors observed in long-term survivors of childhood cancer.

The population rates used to compute expected values may not be strictly applicable. However, it is difficult to imagine how more appropriate rates could change the results significantly, since the expected numbers are so low compared with the observed number of second cancers. There was no difference between the RR of second cancers at North American and European centers (14.8 and 15.5, respectively), lending some support to the use of Connecticut Tumor Registry rates to compute expected values. The major source of bias in our study is probably the cohort selection. The cohort was chosen on the basis of at least 2-year survival and known duration of follow-up, and some survivors lost to follow-up are not included. It is also known that all patients with second tumors do not return to the hospital where they were initially treated, so the observed number of second tumors may be low. Thus in all probability, we have underestimated the risk of second-cancer development, and the estimates might be considered an indication of the minimum risk following childhood cancer.

In children with double primary neoplasms, heritable tumors are among the most common initial cancers. This suggests an interaction between genetic susceptibility and therapy in the development of second cancers. For example, retinoblastoma patients are prone to second primary cancers, especially osteosarcomas (22) at a rate of 1,000 times that of the normal population, and almost all cases with second tumors had bilateral or heritable disease. In addition, one-third of the osteogenic sarcomas occurred outside of the radiation field and two were pinealblastomas. The association between retinoblastoma and pinealblastoma has been previously described as "trilateral retinoblastoma," with pinealblastoma arising from vestigial photoreceptors as a variant of multicentric retinoblastoma (1). Thus, for retinoblastoma, genetic factors may outweigh radiation as the major determinant of the risk of second cancer. It should be noted, however, that children with retinoblastoma seen at large referral centers may be more likely to have bilateral or heritable disease.

Studying childhood cancer provides insights into the radiation sensitivity of organs at different ages. Marshall Islanders showed an elevated risk of thyroid tumors if exposed to radioactive fallout under age 10 (6). In our study group, high rates of thyroid cancer were also seen, especially for childhood tumors

treated at an early age with high doses of radiation, that is, Wilms' tumor, neuroblastoma, and Hodgkin's disease. The median age at diagnosis of first tumor for those developing thyroid cancer was 5 years.

The Ewing's sarcoma patients are noteworthy, since the relative risk of developing osteogenic sarcoma was about 650, similar to the experience of retinoblastoma patients. These results resemble those reported by Greene et al. (9) from the National Cancer Institute and Strong et al. (23) from the M. D. Anderson Hospital. All cases of osteosarcoma following Ewing's tumor were irradiated, and the average age at first diagnosis (and treatment) was 10.9 years. These cases were irradiated mainly during the adolescent growth spurt, when bones might be particularly susceptible to radiation effects. Similar risks of osteosarcoma are seen in children treated for Hodgkin's disease, with a median age of 11.9 years at irradiation. It is interesting that following essentially the same therapy, adults with Hodgkin's disease only rarely develop osteosarcomas (3, 5,24). Thus, the risk of certain second cancers seems to depend on host susceptibility as well as treatment effects.

Our case-control study will examine in detail the potentially carcinogenic effects of radiotherapy and chemotherapy and their interactions. This type of evaluation is especially important in view of changing therapy practices, including a tendency to switch from orthovoltage to megavoltage radiation (11), and to use combination chemotherapy for an increasing number of tumors.

CONCLUSION

What is the significance of these findings? First, long-term survivors of one childhood neoplasm have an elevated relative risk of developing a second cancer, reaching a cumulative risk of 12% by 25 years. The absolute risk is estimated to be 3.1 extra cancers/1,000 persons/year. There is no indication of an overall decrease in the risk of developing a second cancer, even after 25 years of observation. The development of several second cancers, especially osteosarcoma and thyroid cancers, appears to be associated with radiation therapy, and our ongoing case-control study will evaluate to what extent. Each initial cancer has a distinctive array of second tumors, and some combinations appear to reflect underlying genetic syndromes, or host susceptibility to radiation therapy used for the first tumor. Although sex does not appear to influence subsequent risk of developing second malignancies, age at therapy does. Thus, adolescence seems associated with an increased susceptibility to radiogenic osteosarcoma, possibly because of the active bone growth during this period, whereas young children appear especially prone to radiogenic thyroid cancer.

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ADDENDUM

After the preparation of this manuscript, an important publication on second cancers in children appeared from the Late Effects Study Group (18a). Among 14,600 children with cancer, 113 nonreferred cases of second malignancies were evaluated, and the cumulative probability of developing a second cancer was estimated to be 3.3% at 20 years. The difference between this percentage and our estimate of 8.5% at 20 years is explained by different study designs and assumptions. Miké et al. (18a) included all children diagnosed with a first malignancy before 1971 but did not have follow-up information on individuals. To estimate person-years at risk, they assumed that the survival experience of the children was similar to U.S. published rates and that children who did not develop a second malignancy remained disease-free through 1979. On the other hand, we evaluated children who survived 2 or more years after diagnosis of their first malignancy, and abstracted follow-up information on individuals, ending the period at risk of developing a second malignancy at the date last seen by a physician. By making our analysis as comparable to Miké et al. as possible and by assuming that children not known to have developed a second cancer survived and remained disease-free through 1979, our estimated 20-year cumulative risk becomes 3.6%. The assumption that patients lost to follow-up did not develop a second cancer before the closing date of the study is a conservative one; that is, it likely underestimates the actual risk. Our estimate based on actual periods of observation, however, could be an overestimate if children who developed a second cancer were more likely to return for evaluation to the hospital where first treated than children who did not develop a second cancer. The "true" risk estimates for development of second cancers probably lie somewhere between the estimates from our two studies. Regardless, both estimates are quite large when compared with the expected cumulative probability of developing a second cancer at 20 years of 0.54%.

Other differences between the two studies that could also account for variations in risk estimates are that Miké et al. (18a) included children first diagnosed

before 1971, evaluated children in 10 LESG centers, applied Third National Cancer Survey incidence rates for one calendar period (1969–1971) to compute expected values, excluded children diagnosed with retinoblastoma, and included nonmelanoma skin cancers as second malignancies. We included children diagnosed before 1980, evaluated children in 13 LESG centers, applied Connecticut 5-year specific incidence rates for 1945–1979 to compute expected values, included children with retinoblastoma, and excluded nonmelanoma skin cancers as second malignancies.

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